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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,510	09/20/2005	Yukinori Masuda	125413	1359

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OLIFF & BERRIDGE, PLC
P.O. BOX 320850
ALEXANDRIA, VA 22320-4850

EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	
MAIL DATE	**DELIVERY MODE**
01/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,510	MASUDA ET AL.	
	Examiner	Art Unit	
	Charanjit S. Aulakh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is /are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 12/20/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. According to a preliminary amendment filed on Sep. 20, 2005, the applicants have amended claims 5 and 8-24.

2. Claims 1-24 are pending in the application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following eight different factors (see Ex parte Foreman, 230 USPQ at 547; Wands, In re, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed:
Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on atleast four of the above mentioned eight different factors such as quantity of experimentation necessary, the amount of direction or guidance provided, presence of working examples, state of the prior art, unpredictability and the breadth of claims.

In regard to lack of enablement issue of instant claims 1-24 for solvates of instant compounds of formula (1), there is no teaching or guidance present in the specification for preparing any specific solvates. Preparation of specific solvates of any compound is a very specialized field and involves their characterization using different techniques such as infrared spectrum, XRD powder diffraction etc. There is no teaching or guidance present in the specification regarding any specific solvents used for preparing specific solvates and their characterization using any techniques such as XRD powder diffraction or infrared spectrum etc. There is not even a single example present for preparing any specific hydrate or solvate of instant compounds of formula (I). There is lot of unpredictability regarding stability of different solvates of any compound in the art. The instant compounds of formula (1) encompasses hundreds of thousands of compounds based on the values of variables R1, R2, Ra, Rb, X1, X2, Y and Ar and therefore, in absence of such teachings, guidance, presence of working examples and unpredictability, it would require undue experimentation to select specific solvates of instant compounds with enhanced stability properties.

In regard to enablement rejection of claims 9-24 for treating or preventing various disease conditions, the specification teaches that the instant compounds are antagonists of T-type calcium channel in vitro. There is no teaching or guidance present in the specification or prior art that hyperactivity of T-type calcium channel is implicated in the etiology of hypercardia, heart failure, cardiomyopathy, arterial fibrillation, arrhythmia, arterial sclerosis, nephritis, nephropathy, renal disorder, renal insufficiency, edema, inflammation, Hyperaldosteronism, neurogenic pain and epilepsy. There is no

teaching in the prior art that structurally closely related compounds having antagonist activity at T-type calcium channel are well known to have therapeutic utility in treating hypercardia, heart failure, cardiomyopathy, arterial fibrillation, arrhythmia, arterial sclerosis, nephritis, nephropathy, renal disorder, renal insufficiency, edema, inflammation, Hyperaldosteronism, neurogenic pain and epilepsy. There are no working examples present showing efficacy of instant compounds in known animal models of hypercardia, heart failure, cardiomyopathy, arterial fibrillation, arrhythmia, arterial sclerosis, nephritis, nephropathy, renal disorder, renal insufficiency, edema, inflammation, Hyperaldosteronism, neurogenic pain and epilepsy. The instant compounds of formula (1) encompasses hundreds of thousands of compounds based on the values of variables R1, R2, Ra, Rb, X1, X2, Y and Ar and therefore, in absence of such teachings, guidance, presence of working examples and prior art, it would require undue experimentation to demonstrate efficacy of instant compounds in known animal models of hypercardia, heart failure, cardiomyopathy, arterial fibrillation, arrhythmia, arterial sclerosis, nephritis, nephropathy, renal disorder, renal insufficiency, edema, inflammation, Hyperaldosteronism, neurogenic pain and epilepsy and hence their utility for treating these disorders.

In regard to preventing any disease condition, it is well known in the art that the etiology of any disease condition involves multiple mechanisms. Therefore, correcting only one of these several mechanisms such as antagonism of T-type calcium channel in the instant case will not prevent (completely cure) that disease condition.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 9-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 9-24, it is not clear whether the claims are directed to compounds of claim 1 or some methods of treatment using compounds of claim 1. If the claims are directed to methods of treatment then it is not clear what is being treated or administered ?

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masumiya (Eur. J. Pharmacol., cited on applicant's form 1449) in view of Kimura (U.S. Patent 4,535,073).

Masumiya teaches effects of calcium channel antagonists including efonidipine on sinus node and demonstrates that efonidipine appears to suppress selectively the later phase of pacemaker depolarization through inhibition of T-type calcium channel similar to Ni2+ which is reported to inhibit the T-type but not L-type calcium channel (see abstract). Masumiya further teaches that efonidipine inhibited both L-type and T-type calcium channels with roughly equal potencies (see page 20, 2nd column, first paragraph). Masumiya further teaches that one of the therapeutic goals for treating cardiovascular disorders is a decrease in myocardial oxygen consumption through a decrease in heart rate (see page 20, 2nd column, 2nd paragraph). Masumiya meets all the limitations of instant claims except that Masumiya does not link T-type calcium channel antagonist activity with optically active R-form of efonidipine. However, Kimura discloses 1,4-dihydropyridine-3-carboxylate compounds of formula (I) encompassing efonidipine for treating various cardiovascular diseases including hypertension (see col. 1, lines 5-67). Kimura further teaches that the compounds of formula (I) have asymmetric carbon atom and all the optically active compounds and mixtures thereof are within the scope of the present invention and teaches methods for preparing optically active compounds (see col. 5, lines 20-40). Therefore, one skilled in the art would have been motivated to prepare optically active form of efonidipine as taught by Kimura which selectively inhibits T-type calcium channel with reasonable expectation of success since Masumiya

teaches the expected benefit of a decreased heart rate when bradycardia is mainly achieved by prolongation of the diastolic period as observed with T-type calcium channel antagonists (see page 20, 2nd column, 2nd paragraph).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

C. S. Aulakh

Charanjit S. Aulakh
Primary Examiner
Art Unit 1625